Cost-Effectiveness of Scaling Up HCV Prevention and Treatment in the United States for People Who Inject Drugs

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ABSTRACT

Aims: To examine the cost-effectiveness of hepatitis C (HCV) treatment of people who inject drugs (PWID), combined with medication-assisted treatment (MAT) and syringe-service programs (SSP), to tackle the increasing HCV epidemic in the United States.

Design: HCV-transmission and disease progression models with cost-effectiveness analysis using a health care perspective and measuring benefits in quality-adjusted life-years (QALYs).

Setting: Rural Perry County, Kentucky (PC), and urban San Francisco, California (SF),USA. Compared with PC, SF has a greater proportion of PWID with access to MAT or SSP. HCV treatment of PWID is negligible in both settings.

Participants: PWID, data collected between 1998 and 2015 from Social Networks Among Appalachian People, U Find Out, Urban Health Study, and National HIV Behavioral Surveillance System studies.

Measurements: Three intervention scenarios modeled: baseline—existing SSP and MAT coverage with HCV screening and treatment with direct-acting antiviral for ex-injectors only as per standard of care; Intervention 1—scale-up of SSP and MAT without changes to treatment; and Intervention 2—scale-up as Intervention 1 combined with HCV screening and treatment for current PWID. Incremental cost-effectiveness ratios (ICERs) and uncertainty using cost-effectiveness acceptability curves.

Findings: For both settings, Intervention 2 is preferred to Intervention 1 and the appropriate comparator for Intervention 2 is the baseline scenario. Relative to baseline, for PC Intervention 2 averts 1,852 more HCV infections, increases QALYS by 3,095, costs $21.6 million more, and has an ICER of $6,975/QALY. For SF, Intervention 2 averts 36,473 more HCV infections, increases QALYs by 78,93, costs $ 872 million more, and has an ICER of $11,044/QALY. The cost-effectiveness of Intervention 2 was robust to several sensitivity analysis.

Conclusions: Hepatitis C screening and treatment for people who inject drugs, combined with medication-assisted treatment and syringe-service programs, is a cost-effective strategy for reducing hepatitis C burden in the United States.

INTRODUCTION

Hepatitis C virus (HCV) is a blood-borne virus that usually results in life-long chronic infection that can lead to liver disease and death. In 2010, an estimated 3.5 million Americans had chronic HCV infection [1], and in 2015 there were 19,629 deaths reported to CDC with HCV listed on the death certificate [2]. If not addressed, the HCV-associated cost burden will remain substantial. Total healthcare cost associated with HCV infection was $6.5 billion in 2011, with an expected peak in 2024 at $9.1 billion [3].

HCV is primarily transmitted through injection drug use in the United States [4], with a seroprevalence above 50% among people who inject drugs (PWID) [5-8]. Many parts of the United States, particularly rural areas, are experiencing an epidemic of prescription and illicit opioid use, including heroin and fentanyl, with corresponding large increases in HCV infection [9, 10].

A recent treatment revolution brought new direct-acting antiviral treatments (DAAs) for HCV infection, with high efficacy (sustained viral response [SVR] or cure rate > 90%), short duration (8-12 weeks) and few side-effects [11]. Although prices have dramatically declined, the high treatment cost ($26,400 for the cheapest pan-genotype drug approved so far [12]) and the large number needing treatment raise questions of affordability for scaling up treatment rates.

Guidelines recommend infected individuals to be treated [11]. However, payer policies deter HCV treatment for PWID [13]. Medication-assisted treatment (MAT, principally methadone or buprenorphine) and syringe-service programs (SSPs) can reduce the risk of HCV acquisition among PWID. Combining MAT and SSP with HCV treatment can impact both incidence and prevalence of HCV infection, and may be more effective in reducing the transmission of HCV among PWID than any one of those strategies alone [14]. Therefore, a comprehensive approach to

cost-effectiveness assessment necessitates inclusion of comprehensive programs comprised of MAT, SSP and HCV screening and treatment.

The objective of this analysis is to evaluate the cost-effectiveness of scaling up MAT and SSP paired with or without HCV screening and DAA treatment for PWID. We evaluated these interventions in one rural and one urban U.S. setting.

METHODS

Model Description

Our analysis uses two validated dynamic, deterministic, compartmental models of HCV-transmission and disease progression among current and ex-PWID [15]. One model is used for Perry County, Kentucky (PC), and the other is used for San Francisco (SF). The models used for the two locations vary slightly, reflecting different demographics and injecting drug use dynamics. Models were stratified by age (SF) or injection duration (PC); intervention status (MAT, SSP, or no intervention); and low- or high-risk behavior (defined as sharing injection equipment in the past 6 months). The rate of HCV transmission depends on the prevalence of HCV among the PWID population, MAT/SSP status, HCV treatment status, low- or high-risk status, and age or injection duration. Once infected, individuals either spontaneously clear infection or develop life-long chronic infection. However, if diagnosed, most people who are HCV-infected, including PWID, may receive antiviral treatment. People who achieve SVR are no longer infectious but may become re-infected at the same rate as susceptible PWID and can then be re-treated.

Population

We separately modeled the PWID population in urban SF and rural PC. These locations characterize two types of U.S. PWID populations; SF has an older stable population of PWID

who primarily inject heroin with relatively high coverage of SSP and moderate coverage of MAT [16, 17]; whereas PC's PWID population is young and increasing, primarily injects prescription opioids, and has no SSP (after model building an SSP has been in place since April 2, 2018) and limited MAT [5, 18].

Model Parameterization

The PC model used data from the Social Networks Among Appalachian People (SNAP) cohort study [5], which recruited PWID in PC. The model assumed an increasing PWID population size between 1990 and 2000 with an estimated 700 PWID in 2009. At baseline, MAT coverage was assumed to be low (4.7%) with no SSP or HCV treatment for current PWID. In 2009, the HCV seroprevalence among PWID was 53.3% and HCV incidence during follow-up (2008–2015) was 18.3 per 100 person-years (pyrs).

The SF model was parameterized to data from the UFO study [19, 20], the National HIV Behavioral Surveillance System (NHBS) [21], and the Urban Health Study (UHS) [22]. The model assumed an aging (20% of PWID < 30 years old) and slowly decreasing PWID population, with an estimated 30,000 PWID in 2007 [18]. At baseline, MAT coverage was assumed to be low-moderate (12%), with high SSP coverage since the late 90s (84%), but no HCV treatment for current PWID. In the absence of recent data, UHS data from 1998–2000 estimated the HCV seroprevalence among PWID younger than 30 as 60.8%, those 30 to 49 as 93.5%, and those older than 50 as 96.3% [22]. The HCV incidence among PWID younger than 30 years was 25.1 per 100pyrs in 2001, remaining stable since then [23, 24].

For both models, we assume MAT and SSP reduce HCV transmission risk based on a recent Cochrane review [25], by 50% and 56% for MAT and SSP on their own, respectively, and

by 72% if on both (product of the risk ratios). The SVR rate of DAAs was varied between 85-95% (Table 1).

Model Calibration

Five thousand parameter sets were sampled from the parameter uncertainty ranges for each setting. First, each model was initially calibrated to population demographics in each setting, which allowed for injecting increases in the 1990s in PC but decreases in SF. Second both models were fit to the coverage of MAT and SSP in each setting and the proportion of PWID at high risk. Lastly, the PC model was fitted to the HCV seroprevalence among PWID injecting for less than 3 years, and the SF model to the HCV incidence in PWID younger than 30 and seroprevalence in PWID older than 50. Model projections were validated with prevalence in those injecting over three years and HCV incidence in PC, and prevalence in those aged under 30 in SF. More details on model structure, parameterization and calibration are in the accompanying paper and summarized in Appendix 1.

Intervention Scenarios

The time horizon for our analyses was 10 years of intervention (2017–2026) followed by 50-year follow-up (2027–2076) at baseline levels of intervention coverage to capture long-term prevention and morbidity benefits. For our main analysis, we considered three intervention scenarios:

- *Baseline*: Maintain current levels of SSP (0% in PC and 84% in SF) and MAT (4.7% in PC and 12% in SF) with existing HCV care and treatment. This includes usual HCV screening and treatment with DAAs for persons who formerly injected drugs but not for those currently injecting. For persons who formerly injected drugs, this includes annual screening of 2%–10% for persons with asymptomatic disease

(fibrosis stages F0–F3) and 25%–50% for persons with more progressed disease [26-28], followed by treatment of 10%–20% for any diagnosed individual [29-31].

- *Intervention 1 (Scale-up MAT and SSP)*: Scale-up of SSP (only applicable for PC) and MAT to 50% coverage with no change in screening and treatment rates.
- *Intervention 2 (Scale-up MAT and SSP plus HCV treatment for PWID)*: Scale-up of SSP and MAT as for Intervention 1, plus annual screening of 90% of PWID for HCV, followed by treatment with DAAs for 90% of diagnosed PWID.

Costs and Health Outcomes

The perspective on costs was that of the third-party payer (2016 prices). The model included costs for HCV screening with a rapid test, laboratory-confirmatory testing (RNA test) for all positives, and other laboratory tests (markers of liver disease) for all diagnosed individuals [32-35]. Existing studies were used to get the costs of MAT with methadone [36] and the costs of SSP [37]. HCV treatment costs included the current average cost of DAAs and costs for treatment monitoring [11, 33]. The model also included the estimated health care costs associated with different HCV-related disease stages [38], and annual monitoring costs after achieving SVR [38]. Input costs and sources are in Table 1 with more details in Appendix 2.

Main model health outcomes were the number of new HCV infections and quality-adjusted life-years (QALYs). QALYs were estimated using existing Canadian utility weights unadjusted by the Canadian population norm [39, 40], adjusted both to the U.S. population [41], and to account for lower utilities among PWID (than general population) which are heightened among PWID on MAT [42] (see Table 1). All costs and QALYs were discounted at 3% annually.

(Insert Table 1 here)

Cost-Effectiveness Analysis

Incremental cost-effectiveness ratios (ICERs; additional cost to gain one QALY) comparing non-dominated scenarios were estimated [43]. A scenario is dominated (i.e. not cost-effective) if it is more expensive and less effective (strict dominance) than another, or if it has a higher ICER than a more costly intervention (extended dominance)[44]. The preferred scenario is determined by comparing the ICER with what decision makers are willing to pay for an additional QALY. There is no consensus on decision makers' willingness-to-pay (WTP) in the United States, although a threshold of $50,000 to $100,000 per QALY saved has been used elsewhere [45, 46].

Uncertainty in the model projections was assessed using cost-effectiveness acceptability curves (CEACs) to graphically show the probability that each strategy is the most cost-effective based on different WTP thresholds [43, 44]. Uncertainty distributions for each parameter are given in Table 1 (costs and utilities) and Appendix 2 (other parameters). Five thousand parameter draws were randomly sampled from these distributions, and the model was run for each scenario to give a distribution of model outcomes. The analysis conformed to good practice guidelines on cost-effectiveness analyses [47].

Sensitivity Analyses

We conducted 9 one-way sensitivity analyses to test the robustness of our results to variations in key parameters. 1. To account for further reductions in the cost of DAAs due to the recent announcement of generic DAAs [48], we reduced the cost of DAAs by 25%, 50%, and 75%. 2. To analyze the impact of lower DAA effectiveness, the SVR rate was reduced from between 85-95% to between 70% and 80%. 3. The impact of the time horizon of the analysis was assessed by changing it from 60 years to 35 and 110 years (maintaining 10 years of intervention).

4. Intervention 2 includes nearly universal screening (90%) and HCV treatment uptake (90%), based on current guidelines. We considered less favorable assumption for screening (45%) and treatment uptake (45%). 5. We conducted 3 separate sensitivity analysis on our utility values. 5.1 We assessed the impact of using lower utility values, as reported in Wittenberg et al. (2016), for PWID not in MAT (0.574 instead of base-case 0.8), and PWID in MAT (0.722 instead of base-case 0.9). 5.2 We also assessed the impact of using the minimum quality of life estimator with our baseline utility values, which assigns the lower individual value of multiple co-morbid conditions in this population (Wittenberg et al., 2017). 5.3 Finally, we assessed the impact of using both lower utility values and the minimum quality of life estimator. 6. Because the time constraints of pretest counseling make its widespread adoption unlikely, we conducted a sensitivity analysis that excluded the cost of pre-test counseling ($16) from screening costs. 7. To account for the possibility of higher treatment rates for diagnosed persons who formerly injected drugs, we assumed 53.8% of diagnosed persons who formerly injected drugs would be treated [49], instead of the base-case assumptions of only 10-20% [29-31]. 8. To account for a possible lower HCV prevalence in San Francisco, for those older than 50 we changed the base-case value of 96% to 75.6% (64.6% – 86.6%), based on the results of rapid testing from the latest 2018 NHBS round [50, 51] which reported prevalence using voluntary testing. 9. Finally, we assessed the impact of accounting for an increased risk of death in the four weeks before and after starting MAT [52].

To ascertain which parameters were most important in contributing to the uncertainty in the incremental cost and QALYs gained, we performed analyses of covariance (ANCOVA) [53-55]. The proportion of the sum of squares contributed by each parameter was calculated to determine the importance of each parameter on outcome's variability.

RESULTS

Cost-effectiveness Analysis

Table 2 presents the number of infections, QALYs, costs and ICER for each setting. Other base-case outcomes associated with each strategy, including life-years, numbers reached, cumulative number of complications, and disaggregated costs, are in Appendix 3.

In both PC and SF, Intervention 1 is not cost-effective (Intervention 2 is preferred through extended dominance) and the appropriate comparator for Intervention 2 is the baseline scenario. For PC, relative to baseline, Intervention 2 averted 1,852 more HCV infections and gained 3,095 QALYS, for an additional cost of $21.6 million, and an ICER of $6,975 per QALY gained. For SF, relative to baseline, Intervention 2 averted 36,473 more HCV infections and gained 78,939 QALYs, for an additional costs of $ 872 million, and an ICER of $11,044 per QALY gained.

(Insert Table 2)

Figure 1a shows that in PC the baseline scenario is the most cost-effective intervention for WTP values below $6,000 per QALY. For WTP values above $6,000, scale-up of MAT and SSP and HCV screening and treatment for PWID (Intervention 2) becomes most cost-effective and achieves a higher than 95% probability of being cost-effective for WTP values above $19,000 per QALY gained. Figure 1b shows that in SF, the baseline scenario is the most cost-effective intervention for WTP values below $10,000 per QALY, after which Intervention 2 is more cost-effective, achieving a higher than 95% probability of being cost-effective for WTP values above $28,000 per QALY.

(Insert Figure 1 here)

Sensitivity Analyses

For both settings, the ICER for Intervention 2 compared with the baseline scenario was most sensitive to reductions in the cost of DAAs, changes in the time horizon of the analysis, and reductions in screening and HCV treatment uptake (see Figure 2). 1. In both settings, Intervention 2 became even more cost-effective, with ICERs below $5,000/QALY, when using a cost of DAAs similar to the cost of the less expensive DAAs currently in the market (50% below baseline value). 2. Decreasing the SVR rate of DAAs slightly increased the ICER (less cost-effective) in both settings. 3. Increasing the time horizon improved the ICER in SF and PC. Conversely, shortening the time horizon made the intervention less cost-effective. 4. Reducing screening and HCV treatment uptake rates to 45% each, increased the ICER from 6,975/ QALY to $12,240 per QALY in PC, and from $11,044/ QALY to $14,606 per QALY in SF. 5. Using the minimum utility estimator resulted in slightly lower quality of life gains with Intervention 2 because the utility values for those not in MAT are always lower than HCV states, making the quality-of-life benefit from HCV treatment only observable if the individual is on MAT and for the cirrhosis health state and subsequent stages of chronic HCV disease. Nevertheless, for all sensitivity analysis on the QoL estimates, the ICERs were very close to the baseline values. 6. Excluding the cost of pre-test counseling had a minimal impact on the ICERs for both sites. 7. Assuming a higher treatment rate of diagnosed persons who formerly injected drugs, considerably improved the ICER for Kentucky ($4,516/ QALY), and slightly improved the ICER for San Francisco ($10,676/ QALY). 8. Using a lower prevalence of HCV among those older than 50 in SF resulted in a slightly increased ICER of 13,537/ QALY. 9. Accounting for the increased risk of death before and after MAT led to a modest increase in the ICER in both Kentucky ($7,581/ QALY) and San Francisco ($11,338/ QALY).

(Insert Figure 2 here)

In the ANCOVA of costs, uncertainty in the cost of HCV treatment accounted for most (55% in PC and 84% in SF) of the variation in incremental costs in both settings. Uncertainty in the duration of injection (22%) and the HCV seroprevalence among those injecting <3 years (5%) also played an important role in PC. In the ANCOVA of QALYs, uncertainty in the PWID population sizes (26% in PC and 60% in SF), and utility weights associated with being in health states F0 or F1 (41% in PC and 11% in SF in total) were the main factors accounting for the variation in the incremental QALYs in both settings.

DISCUSSION

The current epidemic of opioid abuse in the United States has led to striking increases in HCV infection, particularly due to increasing injection drug use in rural settings [9, 56]. Therefore, targeting PWID for HCV prevention and treatment is critically important for controlling HCV in the United States [57]. Considering an integrated health care strategy in two settings, our results show that scaling up MAT and SSP, combined with HCV screening and treatment for PWID can be a highly cost-effective approach to reversing the increasing HCV incidence in the United States. This applies both in an urban setting with long-standing injection drug use and moderate to high coverage of MAT and SSP interventions, and in a rural setting with recent increases in injection drug use with negligible coverage of harm-reduction interventions. We show that a combined prevention and treatment approach optimizes the HCV prevention benefits achieved, with the expansion of MAT and SSP directly reducing the risk of new infections, while DAA treatments directly reduce the burden of current infection and indirectly reduce the risk of new infections.

The ICER for the combined intervention was $6,975 per QALY for PC and $11,044 per QALY for SF, which by most standards suggests that HCV screening and treatment of current PWID combined with SSP and MAT scale-up is highly cost-effective in reducing current HCV infections and preventing new ones. However, although cost-effective, it is important to note that most intervention costs (HCV screening and treatment among PWID and MAT and SSP scale-up) are upfront while the health care benefits and costs averted occur many years down the line, so the intervention is less cost-effective when viewed over shorter time frames.

Our results are based on model projections and need to be interpreted with the recognition of several simplifying assumptions. First, we restricted our analysis to direct medical costs. We did not consider the effect of HCV treatment on increasing productivity or any extra-hepatic benefits of treatment [58, 59]. We also did not incorporate the beneficial effects of MAT on HIV-transmission or HIV-treatment outcomes [60-62], on decreasing overdose risk,the number of PWID [63], and criminal activity [64], and improving employment status [65]. Including these effects would improve the cost-effectiveness of scaling up HCV treatment and MAT. We also did not account for patient out-of-pocket costs or costs accrued from prolonged life expectancy [66], which would have reduced the cost-effectiveness of our intervention. Impacts of MAT beyond reduction in HCV transmission can be addressed in a model that explicitly incorporates the natural history of opioid use disorder; the current model focuses on the dynamics of HCV infection amongst PWID.

Second, we assumed that the risk of reinfection was equal to that of initial infection. It is possible that PWID may reduce their risk behavior after HCV treatment [67] and also have a lower biological risk of reinfection [68, 69], which could confer prevention effects beyond our predictions.

Third, we did not account for heterogeneity in treatment compliance (e.g., high-risk individuals may be less likely to enter or comply with treatment). These limitations can be addressed in future modeling that uses empirical research on the effect of patient characteristics on HCV treatment access and compliance.

Fourth, our results were subject to limitations in data availability, particularly surrounding SSP costs and parameterizing and calibrating the model. Most importantly, these included limited data on the evolving injecting and HCV epidemic in both PC and SF. Our model projections included uncertainty in these factors, and although they were robust despite this, they could be improved with better data on these factors. Additionally, our baseline scenario for SF assumes no HCV treatment for active PWID. In 2016, SF initiated an aggressive campaign to eliminate HCV that promotes HCV treatment for at-risk groups, including PWID. Treatment rates are increasing, but specific rates for PWID are not available [70].

Recent health economic models for several settings (United Kingdom, Australia, Netherlands) suggest that early HCV treatment for PWID is likely to be cost-effective [71-74]. However, these previous cost-effectiveness analyses were not conducted in a U.S. setting and did not consider the joint impact of scaling up HCV treatment together with MAT and SSP. Other cost-effectiveness analyses of DAA treatment have been conducted in the United States [40, 75]; but none of those analyses focused on treatment of PWID in a community setting. Our study is the first cost-effectiveness analysis of U.S. HCV treatment combined with MAT and SSP for PWID.

Despite the high incidence of HCV in PWID and professional society guidelines and recommendations advocating HCV treatment for PWID [76, 77], few active PWID have received treatment for HCV [77, 78]. Reaching and engaging PWID has challenges associated with the illicit

nature of injecting drug use and stigma, discrimination, and mistrust of health services [78]. However, successful treatment outcomes have been achieved in numerous settings, with integration of HCV care in substance use treatment settings or co-locating primary health care services and behavioral health services, including MAT and SSP, likely enhancing medication adherence [79]. Unfortunately, the cost of new DAA treatments and the high number needing treatment, Medicaid requirements for drug and alcohol abstinence, and restricting treatment to those with late-stage liver disease have curbed the use of HCV treatment as a prevention strategy in the United States. [80, 81]. Recently, competition between different DAA drug manufacturers has resulted in substantial decreases in the costs of HCV medications [11], while Medicaid's ability to negotiate prices and easing of restrictions on treatment [82, 83] bring hope for the feasibility of HCV treatment as prevention in PWID. Also encouraging is the recent declaration by the President's Commission on Combating Drug Addiction and the Opioid Crisis which led the president to declare the country's opioid crisis a national emergency [84]. One of the commission's recommendations is enhancing access to MAT, with such scale-up being an important avenue for a concomitant scale-up in HCV treatment among PWID.

Conclusions

Our study is the first to examine the cost-effectiveness of HCV treatment as prevention in U.S. rural and urban settings. Despite differences in the injecting epidemics, availability of MAT and SSP, and HCV epidemiology in the two settings, scaling up HCV treatment combined with MAT and SSP is a cost-effective approach for reducing HCV transmission in both settings. This finding may support policy change to reduce disparities in the management of HCV infection and encourage support for HCV treatment in PWID to optimize population-level prevention benefits.

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Table 1. Model Parameters: Treatment Effects, Costs and Utilities

Input Parameter	Perry County		San Francisco		Reference
	Value	**Distribution (a,b)**	**Value**	**Distribution (a,b)**	
Effect of MAT, SSP and DAAs					
Relative risk of acquiring HCV while on MAT	0.5	Log-normal (-0.69, 0.013)	0.5	Log-normal (-0.69, 0.013)	Platt et al., 2017 [25]
Relative risk of acquiring HCV while on SSP	0.44	Log-normal (-0.82, 0.094)	0.44	Log-normal (-0.82, 0.094)	Platt et al., 2017 [25]
Relative risk of acquiring HCV while on MAT+SSP	Product of relative risk for MAT and SSP				
DAA SVR rate	85-95%	Uniform	85-95%	Uniform	AASL 2017 [11]
Screening and diagnosis costs, 2016 USD					
Screening with rapid test (negative result)	35	Gamma (15, 2)	28	Gamma (15, 2)	Cipriano et al., 2012 [32]; Medicaid, 2016 [33]; SAMHSA 2016 [35]
Screening with rapid test (positive result) and diagnosis (negative RNA)	105	Gamma (15, 7)	79	Gamma (15, 5)	
Screening with rapid test (positive result) and diagnosis (positive RNA) and labs	569	Gamma (15, 37)	375	Gamma (15, 24)	
MAT and SSP per person costs, 2016 USD					
Methadone treatment, per day	14	Gamma (198, 0)	14	Gamma (198, 0)	Jackson et al., 2015 [36]

SSP, per year	127	Gamma (15, 8)	127	Gamma (15, 8)	Nguyen et al., 2014 [37]; Bluthenthal et al., 2015 [85]; personal communication with Michael Discepola (2016) and Henry Fisher Raymond (2015)
HCV treatment per person costs, 2016 USD					
Antiviral therapy	58,906	Gamma (3, 17381)	59,466	Gamma (3, 17371)	AASL 2017 [11], Medicaid, 2016 [33]
HCV treatment monitoring (12 weeks)	443	Gamma (15, 29)	274	Gamma (15, 18)	
Complications costs					
F0-F4 (without antiviral treatment)	793	Gamma (2, 330)	793	Gamma (2, 330)	Rein et al., 2015 [38]
CC (without antiviral treatment)	1,509	Gamma (9, 161)	1,509	Gamma (9, 161)	
DC (without antiviral treatment)	20,348	Gamma (39, 517)	20,348	Gamma (39, 517)	
HCC	42,833	Gamma (73, 588)	42,833	Gamma (73, 588)	
1 year after liver transplant	200,458	Gamma (80, 2,512)	200,458	Gamma (80, 2,512)	
>1 year after liver transplant	36,203	Gamma (148, 245)	36,203	Gamma (148, 245)	
Annual monitoring cost after SVR	237	Gamma (4, 61)	237	Gamma (4, 61)	

Utilities					
Quality-of-life multipliers for each health state					
IFN-free therapy-related multiplier	0.95	Beta (108, 6)	0.95	Beta (108, 6)	Chong et al. [39]; Chhatwal et al. [40]
F0, F1	0.93	Beta (47, 4)	0.93	Beta (47, 4)	
F2, F3	0.93	Beta (47, 4)	0.93	Beta (47, 4)	
Compensated Cirrhosis	0.9	Beta (31,3)	0.9	Beta (31,3)	
DC	0.8	Beta (12, 3)	0.8	Beta (12, 3)	
HCC	0.79	Beta (11, 3)	0.79	Beta (11, 3)	
First year, post-liver transplant	0.84	Beta (54, 10)	0.84	Beta (54, 10)	
Post SVR	1	Beta (3,834, 4)	1	Beta (3834, 4)	
Quality-of-life multipliers for PWID					
PWID not on MAT	0.8	—	0.8	—	Zaric et al., 2000 [42]
PWID on MAT	0.9	—	0.9	—	
PWID on SSP	0.8	—	0.8	—	Assumed

CC = compensated cirrhosis; DAA= direct-acting antiviral treatments; DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; MAT = medication-assisted treatment; PWID = people who inject drugs; SSP = syringe-service program; SVR = sustained viral response

Table 2. Base-Case Number of New Infections and Cost-Effectiveness Results for Baseline, MAT+SSP scale-up, and MAT+SSP scale-up with HCV Screening and Treatment Scenarios

	Number of New Infections*	Cost (2016 USD)	QALY	ICER (Inc cost/Inc QALY) Intervention 2 vs. baseline**
Kentucky				
Baseline	4,158	$42,870,668	46,779	
Intervention 1 MAT+SSP	3,907	$57,010,657	47,531	
Intervention 2 MAT+SSP+HCV treat PWID	2,306	$64,456,601	49,874	$6,975
San Francisco				
Baseline	42,221	$1,610,582,798	706,637	
Intervention 1 MAT+SSP	41,175	$1,996,599,159	714,536	
Intervention 2 MAT+SSP+HCV treat PWID	5,748	$2,482,369,200	785,576	$11,044

DAA = direct-acting antiviral agent; HCV = hepatitis C virus; ICER = incremental cost-effectiveness ratio; MAT = medication-assisted treatment; QALY = quality-adjusted life-year; SSP = syringe-service program; PWID = people who inject drugs.

*Small impact of MAT+SSP on number of new infections is due to the bounce back in the HCV epidemic in both settings after 10 years of intervention, such that most infections averted become re-infected throughout the 50-year follow-up. HCV treatment achieves more impact in terms of percentage of HCV infections averted in San Francisco due to the much slower bounce back in that epidemic after treatment ceases (Figure A3-1).

** Intervention 1 is not cost-effective because of extended dominance (i.e., the ICER of Intervention 1 vs baseline is higher than the ICER of Intervention 2 versus Intervention 1)

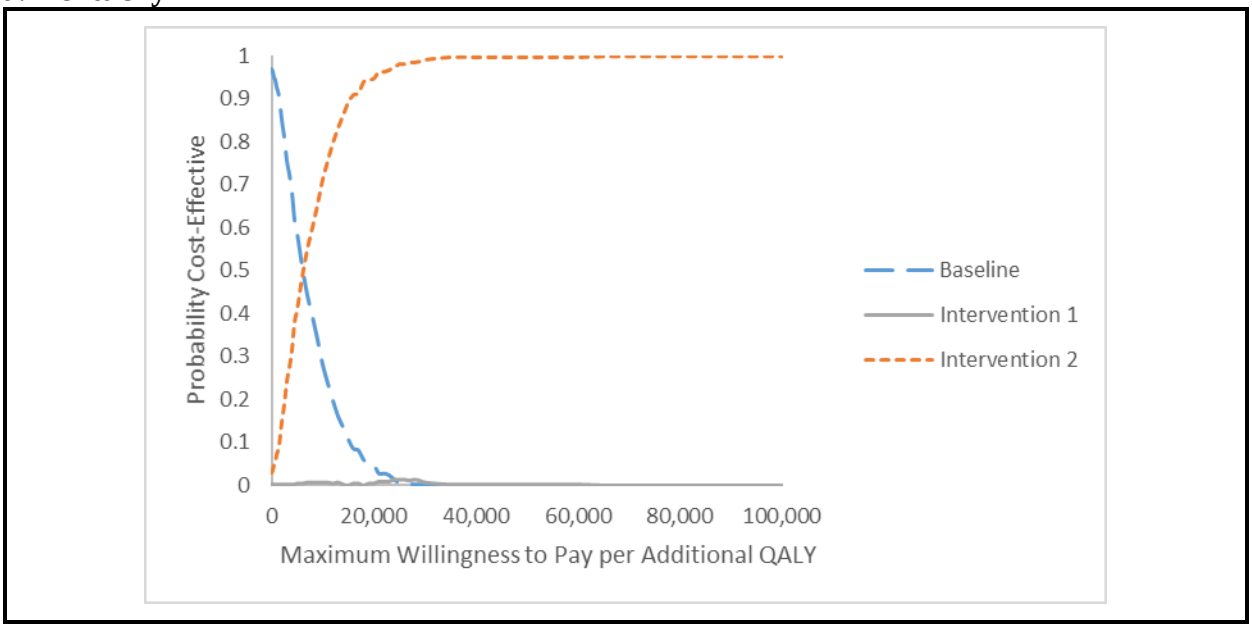
All estimates are over a 60-year time horizon, the scale-up of MAT+SSP and the screening and HCV treatment lasts 10 years; costs and QALYs discounted at 3% annual rate, 2016 prices. Intervention 1 is weakly dominated by Intervention 2 in both settings. Baseline: current levels of SSP and MAT with limited, usual care, annual screening and HCV treatment with DAAs for persons who formerly injected drugs; Intervention 1: scale-up of SSP and MAT to 50% for 10 years with the same level of screening and HCV treatment for persons who formerly injected drugs as in baseline; Intervention 2: scale-up of SSP and MAT, plus annually screening 90% of PWID for HCV, followed by HCV treatment with DAAs for 90% of persons found to be chronically infected.

FIGURES

Figure 1. Base-case results for Kentucky (a) and San Francisco (b) in the form of cost-effectiveness acceptability curves (CEACs).

The CEACs show the probability that one strategy is preferred to the other, for different maximum willingness-to-pay (WTP) for an additional quality-adjusted life-year (QALY). As decision makers are willing to pay more for an additional QALY, the more-costly and effective strategy is preferred. Baseline: current levels of syringe-service program (SSP) and medication-assisted treatment (MAT) with limited, usual hepatitis C virus (HCV) care including HCV screening and treatment with direct-acting antiviral agents (DAAs) for ex-injectors. Intervention 1: Scale-up of SSP and MAT to 50% coverage with the same level of screening and HCV treatment for ex-injectors as in the baseline intervention. Intervention 2: Scale-up of SSP and MAT to 50% coverage, plus annually screening of 90% of current injectors for HCV, followed by HCV treatment with DAAs for 90% of persons found to be chronically infected.

a. Kentucky



b. San Francisco

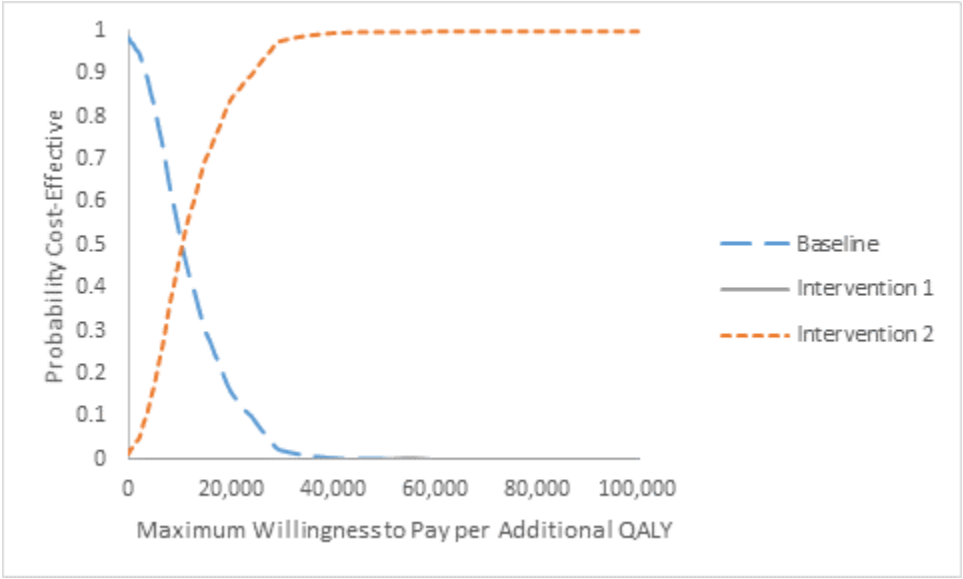
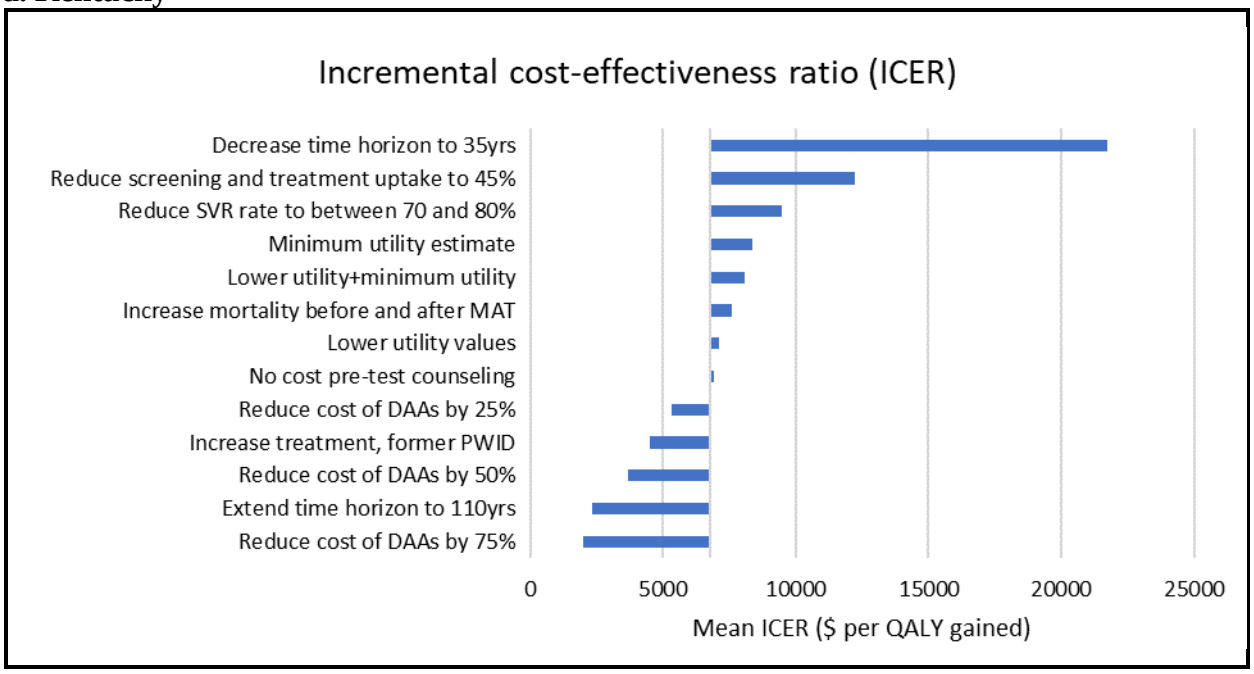


Figure 2. Tornado diagram of univariate sensitivity analyses for Kentucky (a) and San Francisco (b).

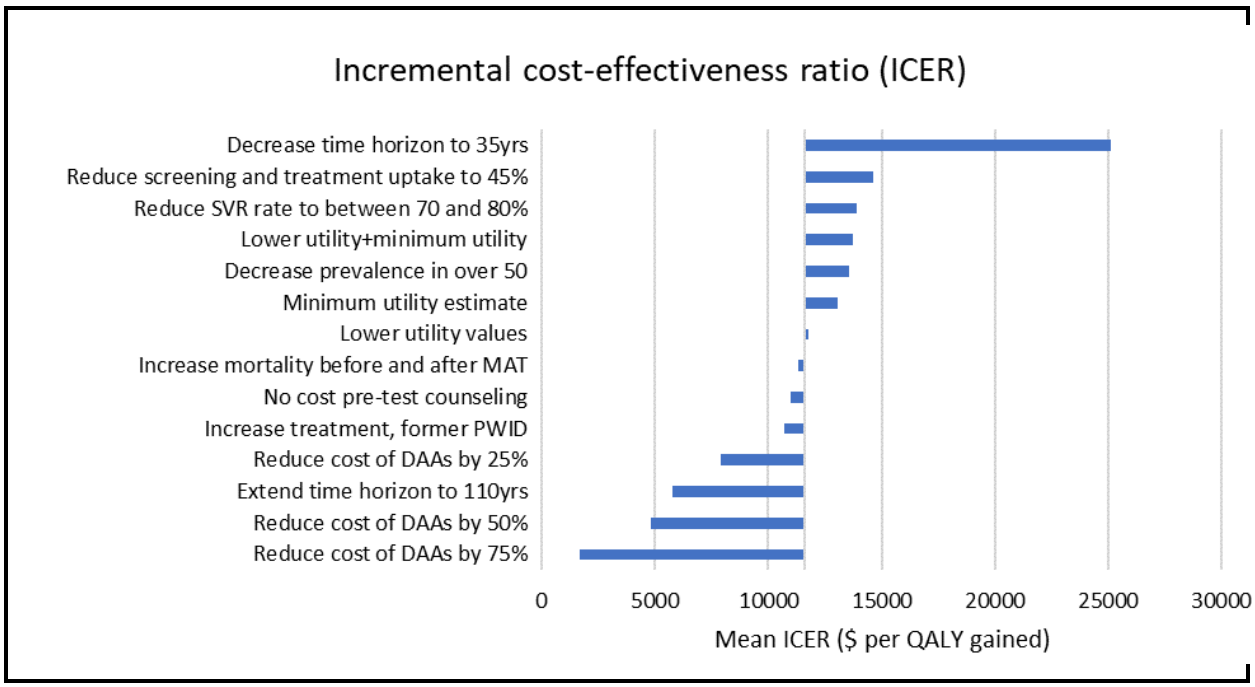
Shows the change in ICERs (horizontal axis; $/quality-adjusted life-year [QALY]) compared to the base-case ICER ($6,975 per QALY for Kentucky and $11,044 per QALY for San Francisco) when different model assumptions are changed (see vertical axis). These analyses consider Intervention 2 where scale-up of MAT and SSP with hepatitis C virus screening and treatment is compared with the baseline scenario. For example, for both settings, Intervention 2 becomes more cost-effective (lower ICER) when reducing the cost of DAAs and less cost-effective (higher ICER) when decreasing the time horizon of the analysis.

a. Kentucky



DAA = direct-acting antiviral agent; SSP = syringe-service program; PWID= people who inject drugs; SVR= sustained viral response; MAT= medication-assisted treatment

b. San Francisco



DAA = direct-acting antiviral agent; SSP = syringe-service program; PWID= people who inject drugs; SVR= sustained viral response; MAT= medication-assisted treatment

APPENDIX

Appendix 1. Model Structure, Epidemiological Inputs and Assumptions

There are two models, one for Perry County and one for San Francisco (models are thoroughly described in a recently accepted publication by Fraser et al. [15]). Both have the same intervention states and risk states (Figure A1-1a), infection states (Figure A1-1b) and disease progression stages (Figure A1-c). However, the PWID demographics and injecting drug use dynamics differed between the sites; with the Perry County (PC) model stratifying by injecting duration (<3 and ≥3 years, Figure A1-d), where PWID injecting <3 years had greater HCV acquisition risk (2.2-fold) compared to those injecting ≥3years, and the San Francisco (SF) model stratifying by age (15-24, 25-29, 30-49 and 50+ years, Figure A1-e) to capture differences in antibody prevalence by age.

Figure A1-1a: Schematic showing the transitions of PWID between different intervention and risk states for both models. PWID in any state can also be in any infection state, injecting duration (Perry County only) or age group (San Francisco only). Note, for clarity demography is not shown. White and black arrows represent movement onto and off SSP, respectively, while mid grey and dark grey represent movement on and off MAT, respectively. Pale grey dashed arrows represent movement from low to high risk, and pale grey arrows with a thick solid line represent movement from high to low risk.

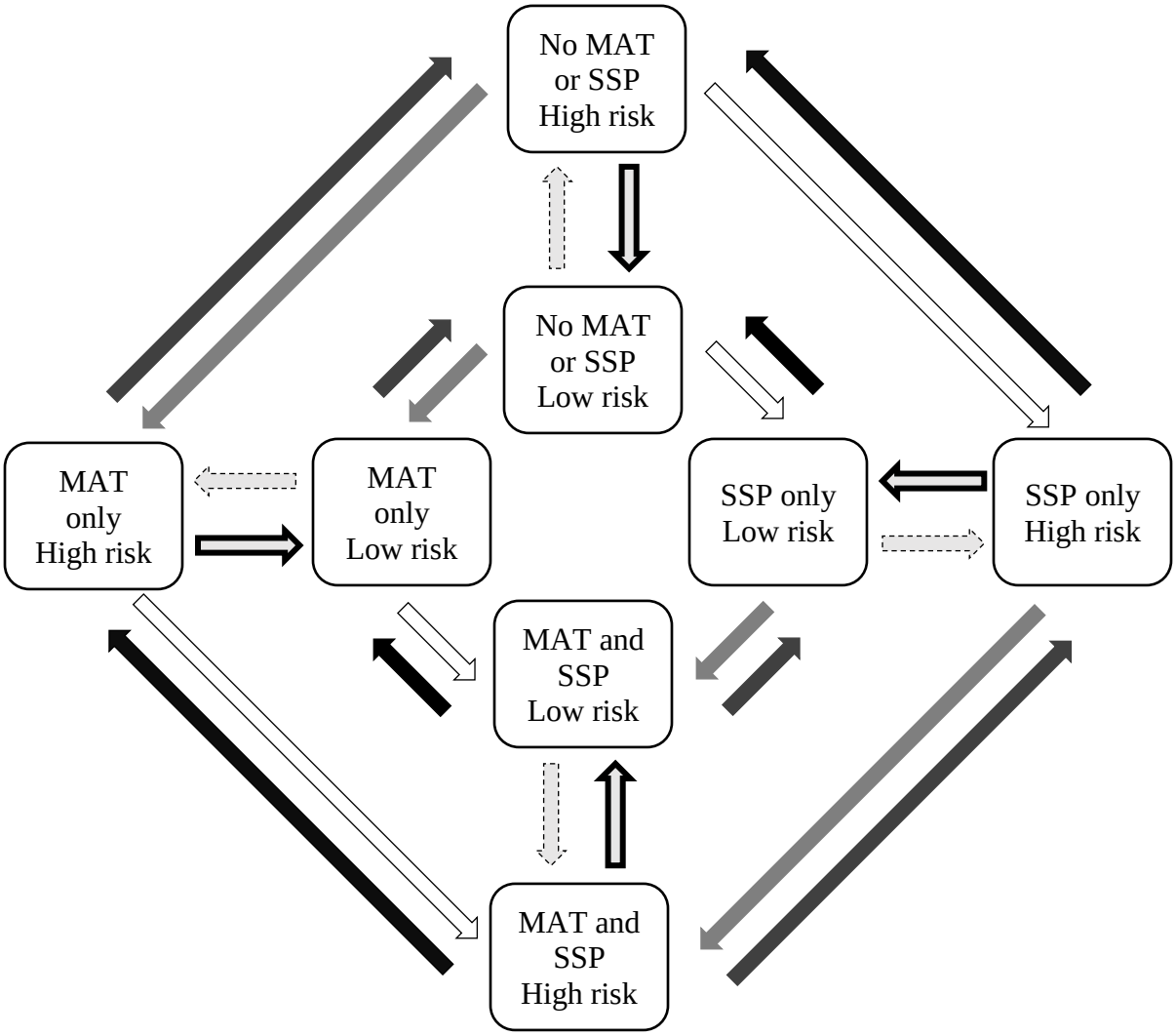


Figure A1-1b: Schematic showing the transitions of PWID between different infections states for both models. A PWID in any state can also be in any injecting duration (Perry County model only), age group (San Francisco model only), intervention or risk state (both models). Note, for clarity demography is not shown.

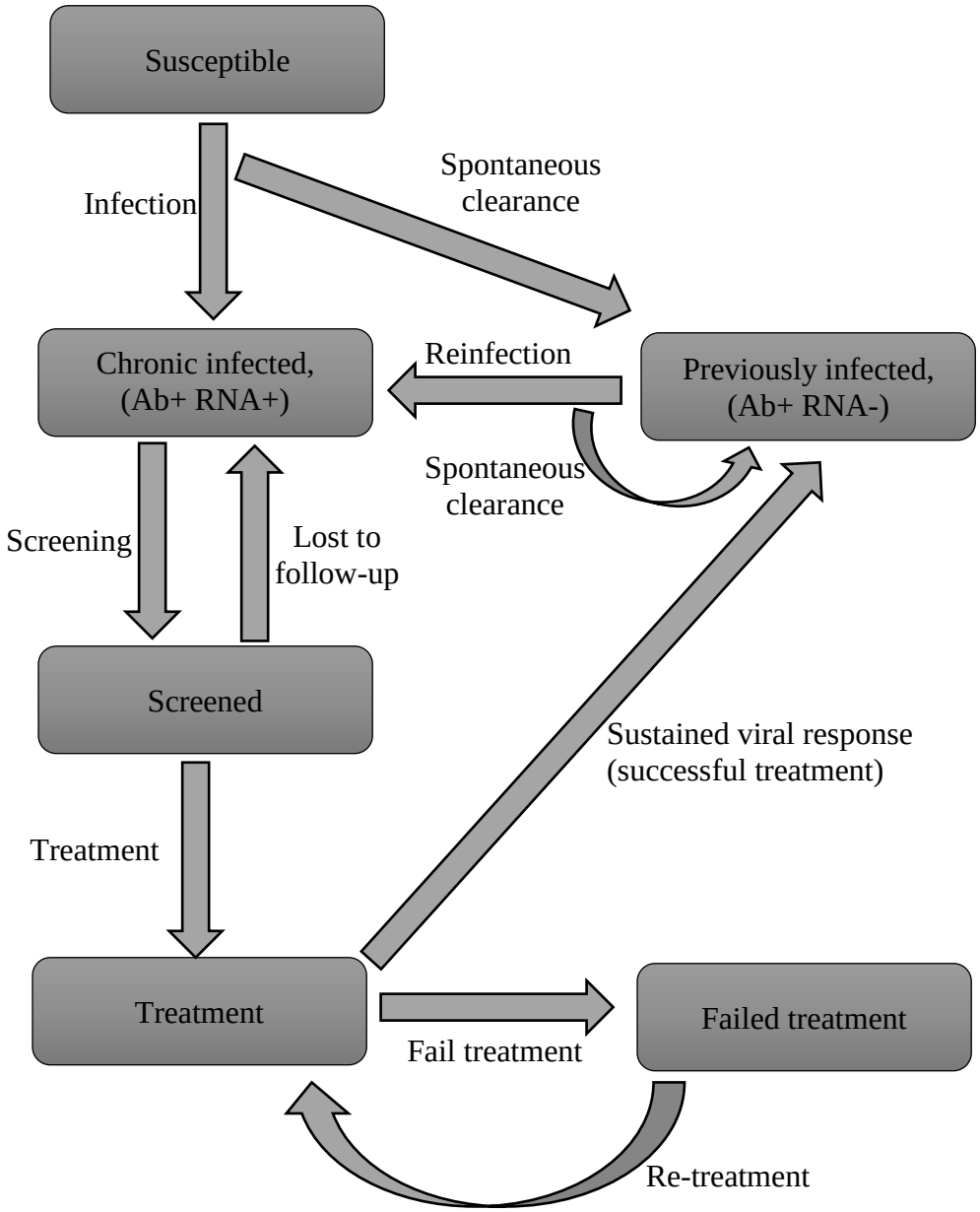


Figure A1-1c: Schematic showing HCV disease progression. Note that no demography is shown unless related to disease progression states. PWID in the susceptible and previously exposed groups do not progress through F_0 to compensated cirrhosis, only chronically infected PWID (both undiagnosed and diagnosed), those in treatment and those who have failed treatment do. From compensated cirrhosis onwards progression amongst susceptible and previously exposed is at a slower rate than those chronically infected or who have failed treatment. A PWID in any state can also be in any injecting duration (Perry County model only), age group (San Francisco model only), risk or intervention state (both models).

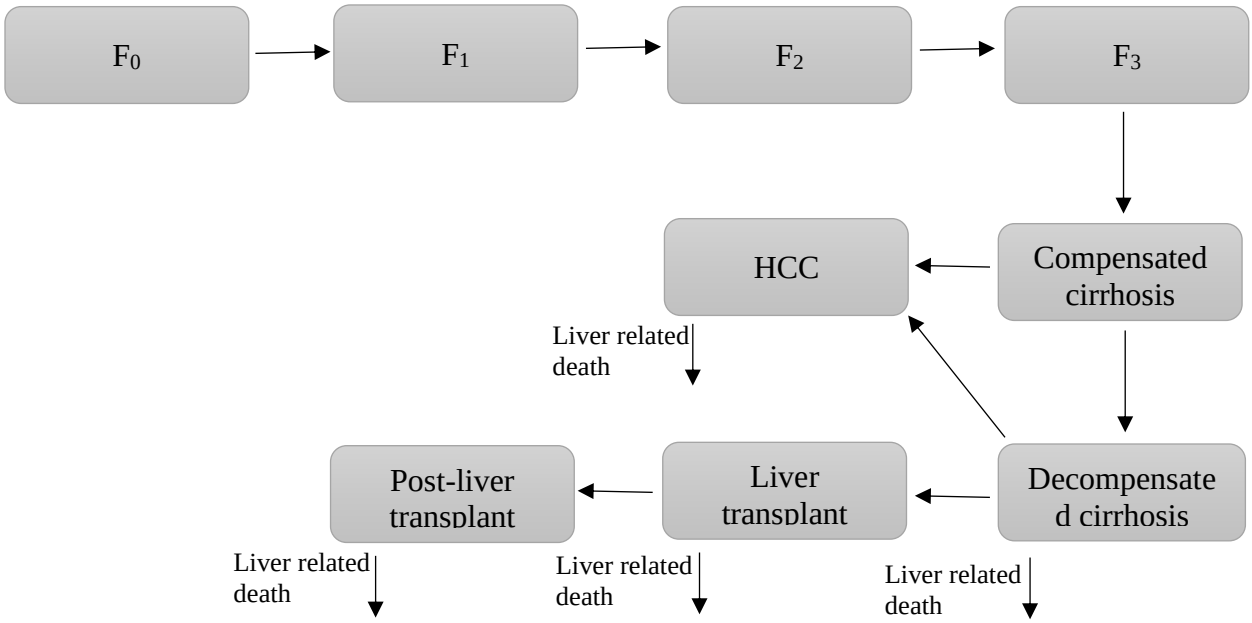


Figure A1-1d: Schematic showing the transitions of current PWID between different injecting duration states for Perry County. A PWID in any state can also be in any intervention, risk state, infection state and disease progression state. Note that those ceasing injecting move to the ex-injector compartment until leaving the model through mortality.

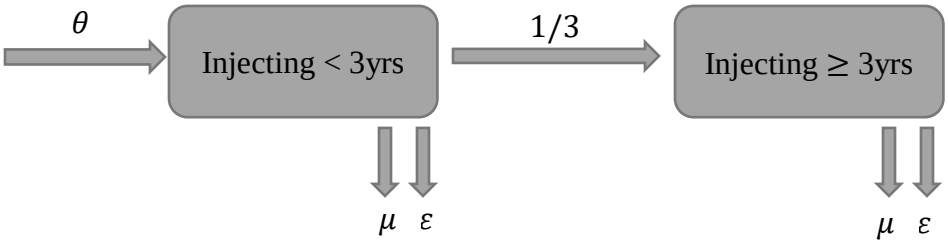
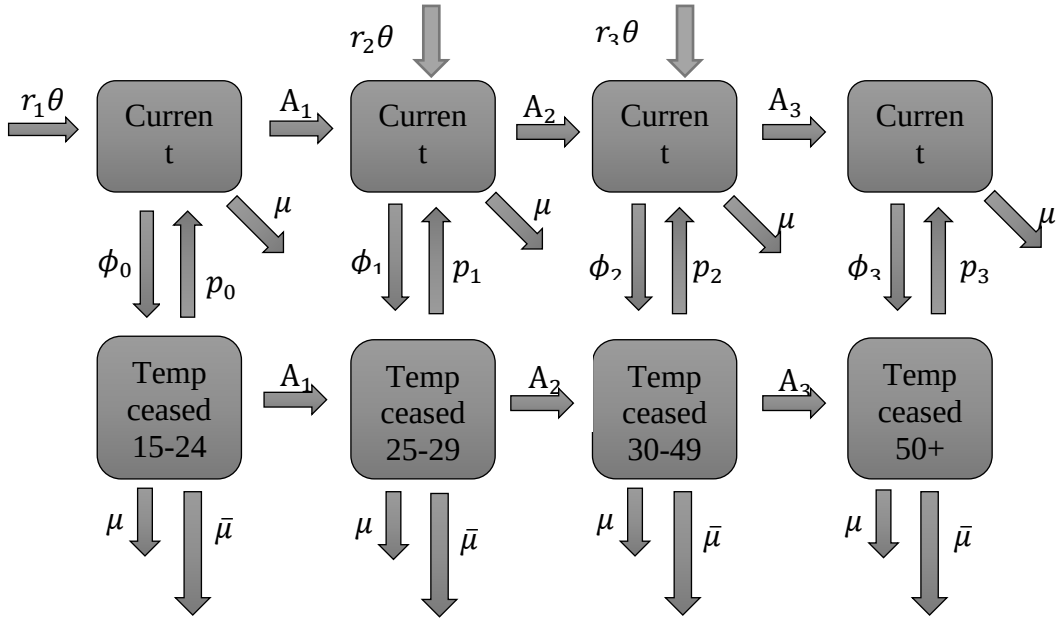


Figure A1-1e: Schematics showing the transitions of current and temporarily ceased PWID between different age and injecting states for San Francisco. A PWID in any state can also be in any intervention state, risk state, infection state and disease progression state. Note that those permanently ceasing injecting from the temporarily ceased group move to the ex-injector compartment until leaving the model through mortality.



Model structure for Perry County, Kentucky

The modeled PWID population was stratified by injecting duration (<3 yrs, ≥3yrs), high and low risk (high risk defined as sharing works in the past 6 months), intervention status (not on MAT or SSP, on MAT or SSP only, or on both), HCV infection status (susceptible, previously infected (Ab+, RNA-), chronically infected (Ab+, RNA+), in treatment and failed treatment), and disease progression status (F0-F3, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (HCC), liver transplant and post-liver transplant) as well as whether a current PWID or ex-injector.

All individuals enter the model as injecting < 3yrs through a time-varying rate of initiating injecting, with a proportion entering as low risk and the remainder as high risk. PWID are able to transition between high- and low-risk states and gradually transition to the injecting three or more years compartment after an average duration of 3 years. PWID that permanently cease injecting move into the ex-injector part of the model, where they are stratified by infection stage and disease progression only. PWID and ex-injectors leave the model from all compartments due to mortality (either drug or non-drug related).

The model simulates HCV transmission at a per-capita transmission rate, which is dependent on the prevalence of chronic infection. HCV transmission risk is reduced if PWID are on MAT, SSP or both, but increased if they are high risk or have been injecting for < 3yrs. We assume that mixing between PWID to form transition contacts can range from random to fully assortative (like-with-like) by duration of injecting and between low and high risk.

All PWID enter the model as F0, susceptible and not on MAT or SSP. Once infected, a proportion spontaneously clear infection and move to the previously infected group, while all other PWID develop chronic infection. Chronically infected PWID remain infected until they are screened and can then be treated, whereupon a proportion achieve a sustained viral response (SVR—effective cure) and the remainder move to the treatment failure group, where they are still chronically infected. We assume those in the treatment failure group can be re-treated.

Once chronically infected PWID progress through disease progression stages at given rates. Those who are treated in the F0-F3 stages and achieve SVR do not progress unless they become re-infected. We assume that PWID who have compensated cirrhosis can progress through disease stages for all infection states, but those who are not chronically infected do so at a slower rate. All individuals with DC or higher disease progression progress at the same rate regardless of infection state.

Model equations for Perry County, Kentucky

The system is modeled by a set of 918 differential equations. There is an additional infection state in the cost-effectiveness model compared to the impact model [15] to account for screening. For current injectors, we denote the variables for the infection states in the model by

$S_{i,j}^{k,l}$ = Susceptible PWID
$E_{i,j}^{k,l}$ = Previously exposed PWID (Ab+, RNA-)
$I_{i,j}^{k,l}$ = Chronically infected PWID (Ab+, RNA+)
$R_{i,j}^{k,l}$ = Screened PWID (chronically infected)
$T_{i,j}^{k,l}$ = PWID in treatment
$F_{i,j}^{k,l}$ = PWID who have failed treatment

where:

- k – injecting duration ($k = 0$ injecting < 3 yrs, $k = 1$ injecting ≥3yrs)
- l – risk status ($l = 0$ low risk, $l = 1$ high risk)
- i, j – MAT and SSP status respectively ($i, j = 0$ not on MAT/SSP, $i, j = 1$ on MAT/SSP).

Post-2017 we assume that a proportion of those chronically infected are screened, and a proportion of those screened are treated; those that are not treated are assumed lost to follow-up and return to the chronically infected compartment.

A susceptible individual can **only** be in disease progression stage F0. This is because if they become infected and spontaneously clear infection they progress to the previously exposed compartment. Therefore, there is no disease progression from this group. Any previously exposed individual can be in any disease progression stage, however **only progresses** through the disease progression stages if in the compensated cirrhosis or more severe compartments. When in the previously exposed compartment, those with compensated cirrhosis progress to decompensated cirrhosis or HCC at a slower rate than those with chronic HCV infection.

For individuals in any infection state $Y_{i,j}^{k,l}$ let us add two additional superscripts m and l (i.e. $Y_{i,j}^{k,l,m,n}$) where

- m represents disease progression: $m = 0$ F0; $m = 1$ F1; $m = 2$ F2; $m = 3$ F3; $m = 4$ compensated cirrhosis (CC); $m = 5$ decompensated cirrhosis (DC); $m = 6$ Hepatocellular carcinoma (HCC); $m = 7$ Liver transplant and $m = 8$ post-liver transplant.

n represents current ($n = 0$) or ex-injector ($l = 1$).

For current injectors in exposed compartments with injecting duration k, risk state l and intervention states i, j, disease progression is modeled by

$$\begin{bmatrix} \dot{E}_{i,j}^{k,l,0,0} \\ \dot{E}_{i,j}^{k,l,1,0} \\ \dot{E}_{i,j}^{k,l,2,0} \\ \dot{E}_{i,j}^{k,l,3,0} \\ \dot{E}_{i,j}^{k,l,4,0} \\ \dot{E}_{i,j}^{k,l,5,0} \\ \dot{E}_{i,j}^{k,l,6,0} \\ \dot{E}_{i,j}^{k,l,7,0} \\ \dot{E}_{i,j}^{k,l,8,0} \end{bmatrix}$$

$$= \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -e_{4a}s_{4a} - e_{5b}s_{5b} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & e_{4a}s_{4a} & -(s_{5a} + s_{5b} + \mu_5) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & e_{4b}s_{4b} & s_{5a} & -(s_6 + \mu_6) & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & s_{5b} & s_6 & -(s_7 + \mu_7) & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & s_7 & -\mu_8 \end{bmatrix} \begin{bmatrix} E_{i,j}^{k,l,0,0} \\ E_{i,j}^{k,l,1,0} \\ E_{i,j}^{k,l,2,0} \\ E_{i,j}^{k,l,3,0} \\ E_{i,j}^{k,l,4,0} \\ E_{i,j}^{k,l,5,0} \\ E_{i,j}^{k,l,6,0} \\ E_{i,j}^{k,l,7,0} \\ E_{i,j}^{k,l,8,0} \end{bmatrix}$$

where s_m represents the rate of progression from disease state m to disease state $m + 1$, s_m represents the decrease in rate of progression from CC to either DC or HCC if not chronically infected and μ_m represents the additional mortality in disease stage m due to being in an advance disease progression stage.

For current injectors in any infected compartments disease progression is therefore modeled by

$$\begin{bmatrix} \dot{X}_{i,j}^{k,l,0,0} \\ \dot{X}_{i,j}^{k,l,1,0} \\ \dot{X}_{i,j}^{k,l,2,0} \\ \dot{X}_{i,j}^{k,l,3,0} \\ \dot{X}_{i,j}^{k,l,4,0} \\ \dot{X}_{i,j}^{k,l,5,0} \\ \dot{X}_{i,j}^{k,l,6,0} \\ \dot{X}_{i,j}^{k,l,7,0} \\ \dot{X}_{i,j}^{k,l,8,0} \end{bmatrix}$$

$$= \begin{bmatrix} -s_0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ s_0 & -s_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & s_1 & -s_2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & s_2 & -s_3 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & s_3 & -s_{4a} - s_{5b} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & s_{4a} & -(s_{5a} + s_{5b} + \mu_5) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & s_{4b} & s_{5a} & -(s_6 + \mu_6) & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & s_{5b} & s_6 & -(s_7 + \mu_7) & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & s_7 & -\mu_8 \end{bmatrix} \begin{bmatrix} X_{i,j}^{k,l,0,0} \\ X_{i,j}^{k,l,1,0} \\ X_{i,j}^{k,l,2,0} \\ X_{i,j}^{k,l,3,0} \\ X_{i,j}^{k,l,4,0} \\ X_{i,j}^{k,l,5,0} \\ X_{i,j}^{k,l,6,0} \\ X_{i,j}^{k,l,7,0} \\ X_{i,j}^{k,l,8,0} \end{bmatrix}$$

where X represents disease stages I, R, T, F.

For ex-injectors, we only track infection stage and disease progression; individuals leaving injecting in any risk, intervention state and injecting duration progress into the corresponding infection and disease progression stage. We assume treatment, screening and disease progression occur in a similar manner to among current injectors.

Model structure for San Francisco

The modeled PWID population for San Francisco was stratified by intervention status, HCV infection and high-risk status in the same way as Kentucky. However, the PWID population in San Francisco was stratified by age categories (15-24year olds, 25-29years olds, 30-49years olds

and 50+year olds) instead of injecting duration, and PWID were stratified by whether they are currently injecting or temporarily ceased injecting. Therefore, individuals move from the temporarily ceased compartments to ex-injector compartments only (ie we assume current PWID have to have a period of temporary cessation before permanently ceasing injecting).

Individuals enter the modeled population as current injectors into the first three age groups through a time-varying rate of initiating injecting, and gradually transition through the age groups. We assume a decrease in the recruitment rate of PWID to fit to the aging PWID population in San Francisco and assume this decrease occurred between 10 and 30 years ago. PWID that are currently injecting can temporarily cease injecting at an age dependent rate. Temporarily ceased injectors can either relapse back to injecting or permanently cease injecting, transitioning to the ex-PWID groups. All individuals in the model (both injectors and ex-PWID) can leave the model through mortality.

HCV transmission occurs in the same way as for the Kentucky model with HCV transmission risk being reduced for the different intervention states, but increased if they are high risk or young. Infection states and disease progression also occur in the same way as for Kentucky. Therefore, the disease progression shown for Kentucky, adapted for the different states in the San Francisco model, can be used to model disease progression in San Francisco.

Appendix 2. Additional Information on Cost Inputs

Screening and diagnosis

HCV screening and diagnosis followed the guidelines issued by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) (http://www.hcvguidelines.org/). The guidelines followed the Centers for Disease Control and Prevention (CDC)–recommended testing sequence for identifying current hepatitis C virus (HCV) infection, where if the HCV antibody test is reactive, there should be further RNA testing and linkage to care if RNA testing is positive. The HCV antibody detection was assumed to be performed with a rapid test, which is more frequently used in medication-assisted therapy (MAT) and syringe services program (SSP) settings and with a population of people who inject drugs (PWID). The lab tests performed after a positive RNA test were informed by the guidelines and selected with CDC advice. Costs were generated for three possible scenarios: (1) screening with rapid test (negative result); (2) screening with rapid test (positive result) and diagnosis with a negative RNA test; and (3) screening with rapid test (positive result), diagnosis with a positive RNA test, and associated laboratory work. The specific components of each scenario are presented in Table A2-1. Costs of pre- and post-test counseling come from Cipriano et al. [32] and are based on CDC estimates. Costs were inflated to 2016 USD using the Bureau of Labor Statistics' Consumer Price Index for medical care services, 2000–2016. The costs associated with alcohol, or substance abuse structured screening and brief intervention services are from the 2016 Medicare fee schedules. All other costs associated with screening and diagnosis are from the 2016 Medicaid fee schedules for each location (Table A2-1).

Table A2-1. Calculations of Screening and Diagnosis Costs

Input Parameter	Cost (2016)		Reference
	Kentucky	San Francisco	
Screening with rapid test (negative result)	$35	$28	
Cost of pre-test counseling	$16	$16	Cipriano, 2012 [32]
Cost per HCV antibody test	$19	$13.00	Medicaid, 2016 [33]
Screening with rapid test (positive result) & diagnosis (negative RNA)	$105	$79	
Cost of pre-test counseling	$16	$16	Cipriano, 2012 [32]
Cost per HCV antibody test	$19	$13	Medicaid, 2016 [33]
Cost of collection of venous blood by venipuncture	$3	$3	
Cost per HCV RNA test	$58	$39	
Cost of post-test counseling, negative result	$9	$9	Cipriano, 2012 [32]
Screening with rapid test (positive result) & diagnosis (positive RNA) & labs	$569	$375	
Cost of pre-test counseling	$16	$16	Cipriano, 2012 [32]
Cost per HCV antibody test	$19	$13	Medicaid, 2016 [33]
Cost of collection of venous blood by venipuncture	$3	$3	
Cost per HCV RNA test	$58	$39	
Cost of post-test counseling, positive result	$17	$17	Cipriano, 2012 [32]
Cost of comprehensive metabolic panel	$11	$9	Medicaid, 2016 [33]
Cost of hepatitis B surface antigen	$14	$9	
Cost of hepatitis B surface antibody	$15	$10	
Cost of EIA or ELISA HIV-1/HIV-2 screening test	$19	$12	

Input Parameter	Cost (2016)		Reference
	Kentucky	San Francisco	
Cost of hepatitis A antibody	$17	$11	
Cost of alcohol and/or substance abuse structured screening and brief intervention services; 15 to 30 minutes	$29		Medicare, 2016 [35]
Cost of HCV genotype test	$351	$236	Medicaid, 2016 [33]

EIA= enzyme immunoassay; ELISA= enzyme-linked immunosorbent assay; HCV= hepatitis C virus.

MAT and SSP

Two strategies to manage injecting opioid use were considered: syringe services programs (SSPs) and medication-assisted therapy (MAT). Using data from the Beth Israel Medical Center/North American Syringe Exchange Network Survey, Nguyen et al. [37] estimated the programmatic costs for a limited set of services provided by SSPs, including syringe exchange, referrals to off-site services, and "no more than one additional on-site service," such as condom distribution, to calculate the average cost per syringe provided by SSPs. We inflated their estimate to 2016 USD, using the BLS Consumer Price Index for medical care services, giving us a cost of $0.56 per syringe.

Data on the prevalence of SSP use among PWID in San Francisco was taken from Bluthenthal et al. [85], who recruited a cohort of 696 current PWID in Los Angeles and San Francisco to study the characteristics of late initiates to drug injection. Through personal communications with Henry Fisher Raymond, PhD, San Francisco Department of Public Health (September 25, 2015) and Michael Discepola, MA, Director of Behavioral Health Services, San Francisco AIDS Foundation (May 24, 2016), we obtained estimates of the number of PWID and the number of syringes exchanged by SSPs in San Francisco in 2015, respectively. Using this data, we calculated the number of syringes exchanged per person per year and multiplied this

number by the cost per syringe to estimate the total cost per person per year of SSPs. Because SSPs have not been in operation long enough in Kentucky to produce sufficient data, we applied the cost per person per year from San Francisco to Kentucky (Table A2-2).

Table A2-2. Calculations of Costs of SSP per Person per Year

Parameter	Value	Source
Unit cost per syringe exchanged in NEP	$0.56	Nguyen et al., 2014 [37]
Number of syringes per person per year	227.57	Calculated
Total number of syringes exchanged	3,845,307	Personal communication with Michael Discepola, 2016
Estimated prevalence of SSP use by PWID	75.10%	Bluthenthal, 2015 [33]
Number of PWID	22,500	Personal communication with Henry Fisher Raymond, 2015
Cost per person per year	$126.67	Calculated

PWID= people who inject drugs; SSP= syringe services program.

Notes: Estimates might not add up due to rounding. The number of syringes per person per year = total number of syringes exchanged / (estimated prevalence of SSP use by PWID * number of PWID). All costs in 2016 prices.

In the United States, the Substance Abuse and Mental Health Services Administration certifies opioid treatment programs (OTPs) to provide MAT with methadone, buprenorphine, and extended-release naltrexone (Vivitrol®), the only three opioid medications approved for the treatment of opioid addiction. We assumed MAT was provided with methadone. The National Survey of Substance Abuse Treatment Services (N-SSATS) found that of the 343,180 clients receiving medication-assisted opioid therapy in OTPs, 96 percent (330,308) received methadone, 4 percent (12,513 clients) received buprenorphine, and less than 1 percent (359) received Vivitrol® [86]. The cost per day of methadone treatment per patient was taken from Jackson et al.

[36]. The authors conducted an analysis of a sample of 11 state Medicaid programs and single state agencies, selected for geographic and population variation.

HCV treatment

Treatment costs consist of the costs of antiviral therapy and treatment monitoring. To estimate the cost of a course of antiviral therapy, we first determined the distributions of four common HCV genotypes (1a, 1b, 2, and 3) among PWID populations in San Francisco and Kentucky. Dias et al. [87] provided data on genotype distributions in San Francisco by conducting a pooled analysis of three data sources: the Urban Health Study (UHS), the U Find Out study, and the Study of the Consequences of the Protease Inhibitor Era. Young et al. [88] described characteristics of a cohort of PWID in the Social Networks among Appalachian People (SNAP) study. We aggregated the data presented by these authors into four genotypes.

We next determined the average costs of treatment for each of the four genotypes. We followed the guidelines issued by the AASLD and the IDSA (http://www.hcvguidelines.org/) for the treatment of HCV, which rate treatment options by strength of evidence. For each genotype, we compiled a list of treatment options, for treatment-naïve patients, with evidence derived from multiple randomized control trials or meta-analyses. We then obtained the costs associated with each of these treatments [89], and took the mean value across all treatments for each genotype. We calculated an average cost of treatment for each location (San Francisco and Kentucky) by weighting the cost for each genotype with the proportion of PWID in each location with that genotype (Table A2-3).

Table A2-3. Calculations of Costs of Antiviral Therapy

Parameter	Value		Source
	San Francisco	Kentucky	
Genotype distributions			
Genotype 1a	51.20%	69.47%	Young, 2012 [88]; Dias et al 2011 [87]
Genotype 1b	22.94%		
Genotype 2	10.22%	16.84%	
Genotype 3	15.64%	13.68%	
Average cost of treatment, genotype 1a	$62,565	$62,565	
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) 12 weeks	$54,600	$54,600	
Daily fixed-dose combination of glecaprevir (300 mg)/pribentasvir (120 mg) for 8 weeks	$26,400	$26,400	
Daily fixed-dose combination of ledispavir (90 mg)/sofosbuvir (400 mg) for 12 weeks	$94,500	$94,500	
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks	$74,760	$74,760	
Average cost of treatment, genotype 1b	$62,565	$62,565	
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks	$54,600	$54,600	
Daily fixed-dose combination of glecaprevir (300 mg)/pribentasvir (120 mg) for 8 weeks	$26,400	$26,400	
Daily fixed-dose combination of ledispavir (90 mg)/sofosbuvir (400 mg) for 12 weeks	$94,500	$94,500	
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks	$74,760	$74,760	
Average cost of treatment, genotype 2	$50,580	$50,580	
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for 8 weeks	$26,400	$26,400	
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks	$74,760	$74,760	

Parameter	Value		Source
	San Francisco	Kentucky	
Average cost of treatment, genotype 3	$50,580	$50,580	
Daily glecaprevir (300 mg)/pibrentasvir (120 mg) for 8 weeks	$26,400	$26,400	
Daily sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks	$74,760	$74,760	
Total cost for course of treatment	$59,466	$58,906	
Genotype 1a	$32,033	$43,466	
Genotype 1b	$14,353	$0	
Genotype 2	$5,169	$8,519	
Genotype 3	$7,911	$6,921	

Note: Estimates might not add up due to rounding.

Using the AASLD and IDSA guidelines and CDC input, treatment-monitoring activities included weekly clinic visits during up to 12 weeks of treatment; lab tests (e.g., complete blood count, creatinine level, calculated glomerular filtration rate, hepatic function panel) every 4 weeks during up to 12 weeks of treatment; and two HCV viral load testing. We costed each monitoring activity using 2016 Medicaid fee schedules for each location (Table A2-4).

Table A2-4. Calculations of Costs of Treatment Monitoring (12 Weeks)

	Value		
	San Francisco	**Kentucky**	**Source**
Cost of clinic visits as clinically indicated to ensure medication adherence and to monitor for adverse events and potential drug-drug interactions (established patient 10-minute office visit; assume one per week)	$11	$20	Medicaid, 2016 [33]
Cost of complete blood count, creatinine level, calculated glomerular filtration rate, and hepatic function panel after 4 weeks of treatment and as clinically indicated (assume three times during 12-week period)	$20	$27	
Cost of blood count; complete (CBC), automated (Hgb, HCT, RBC, WBC, and platelet count) and automated differential WBC count	$6	$9	Medicaid, 2016 [33]
Cost of BUN/creatinine ratio (calculated), calcium, carbon dioxide, chloride, creatinine with GFR estimated, glucose, potassium, sodium, urea nitrogen (BUN)	$7	$9	
Cost of albumin, bilirubin (total), bilirubin (direct), phosphatase (alkaline), protein (total), transferase (alanine amine, SGPT), transferase (aspartate amino, SGOT)	$7	$9	
Cost of quantitative HCV viral load testing after 4 weeks of therapy and at 12 weeks following completion of therapy	$39	$58	
Total cost of monitoring	$274	$443	

BUN= blood urea nitrogen; CBC= complete blood count; GFR= glomerular filtration rate; HCV= hepatitis C virus; HCT= hematocrit blood test; Hgb= hemoglobin; RBC= red blood cell; SGOT= serum glutamic-oxaloacetic transaminase; SGPT= serum glutamic-pyruvic transaminase; WBC= white blood cell.

Notes: Estimates might not add up due to rounding. We assumed one office visit per week during the full course of treatment, lab tests every 4 weeks during the full course of treatment, and HCV quantification at 4 and 12 weeks.

Appendix 3. Additional Results

Table A3-1. Additional Base-Case Results for Baseline, MAT+SSP scale-up, and MAT+SSP scale-up with HCV Screening and Treatment Scenarios

	Kentucky			San Francisco		
	Baseline	**MAT+SSP**	**MAT+SSP with HCV Screen and Treatment**	**Baseline**	**MAT+SSP**	**MAT+SSP with HCV Screen and Treatment**
Number screened	8,750	8,662	21,950	105,068	104,281	384,951
Total number treated	679	618	694	8,008	7,816	20,798
Total number achieving SVR	610	556	623	7,186	7,013	18,652
Number years with CC	10,770	10,041	2,034	274,329	269,420	134,353
Number years with DC	1,363	1,247	190	41,295	40,614	7,306
Number years with HCC	198	181	29	5,341	5,246	793
Number liver transplants	37	33	5	1,094	1,076	200
Number years post-transplant	332	302	45	14,333	14,174	4,750
Number infections	4,158	3,907	2,306	42,221	41,175	5,748
Cost screening*	938,626	851,049	1,385,024	8,331,153	8,171,788	24,405,420
Cost MAT*	5,906,330	22,938,918	22,988,036	407,944,927	808,054,475	823,057,383
Cost SSP*	0	466,989	467,363	56,127,085	56,145,101	57,912,045

	Kentucky			San Francisco		
	Baseline	**MAT+SSP**	**MAT+SSP with HCV Screen and Treatment**	**Baseline**	**MAT+SSP**	**MAT+SSP with HCV Screen and Treatment**
Cost DAA treatment*	13,178,781	11,785,311	33,622,589	175,487,951	171,599,544	1,161,359,076
Cost DAA treatment monitoring*	161,096	144,001	408,794	818,081	799,936	5,389,938
HCV-related complication care costs*	22,294,746	20,486,545	4,204,914	959,277,334	949,304,935	367,030,561
Costs SVR*^	391,090	337,844	1,379,880	2,596,267	2,523,380	43,214,777
Total costs*	42,870,668	57,010,657	64,456,601	1,610,582,798	1,996,599,159	2,482,369,200
Total QALYs	46,779	47,531	49,874	706,637	714,536	785,576
Total life-years	159,704	160,869	165,071	2,273,503	2,275,970	2,450,136

*2016 USD; ^ Costs of SVR are the annual monitoring costs after an individual achieves SVR (Rein et al., 2015).

CC = compensated cirrhosis; DAA = direct-acting antiviral agent; DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; MAT= medication-assisted treatment; QALY = quality-adjusted life-year; SSP = syringe services program; SVR = sustained virologic response.

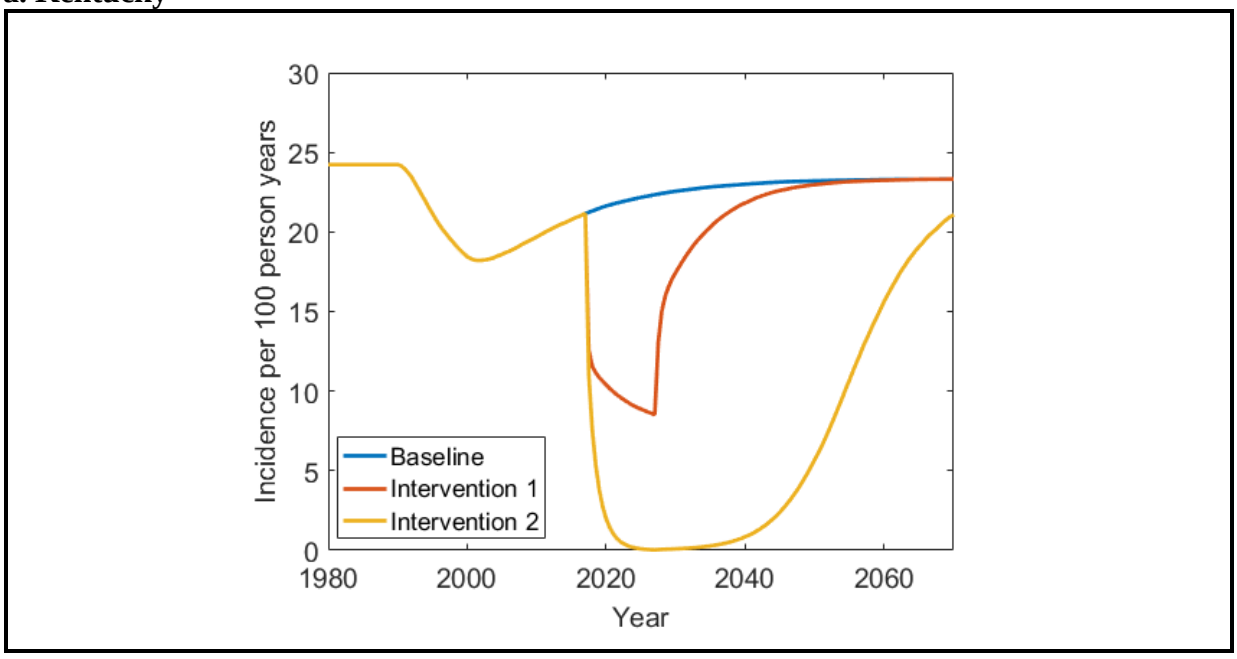
All estimates are over a 60-year time horizon, costs and QALYs discounted at 3% annual rate, 2016 prices. Baseline: current levels of SSP and MAT with limited, usual care, annual screening and HCV treatment with DAAs for ex-injectors; Intervention 1: scale-up of SSP and MAT to 50% for 10 years with the same level of screening and HCV treatment for ex-injectors as in baseline; Intervention 2: scale-up of SSP and MAT,

plus annually screening 90% of current injectors for HCV, followed by HCV treatment with DAAs for 90% of persons found to be chronically infected. The scale-up of MAT+SSP and the screening and HCV treatment lasts 10 years.

Figure A3-1. Number of Infections for Baseline, MAT+SSP scale-up (Intervention 1), and MAT+SSP scale-up with HCV Screening and Treatment (Intervention 2) for Kentucky (a) and San Francisco (b)

Small impact of MAT+SSP on number of new infections is due to the bounce back in the HCV epidemic in both settings after 10 years of intervention, such that most infections averted become re-infected throughout the 50-year follow-up. HCV treatment achieves more impact in terms of percentage of HCV infections averted in San Francisco due to the much slower bounce back in that epidemic after treatment ceases

a. Kentucky



b. San Francisco

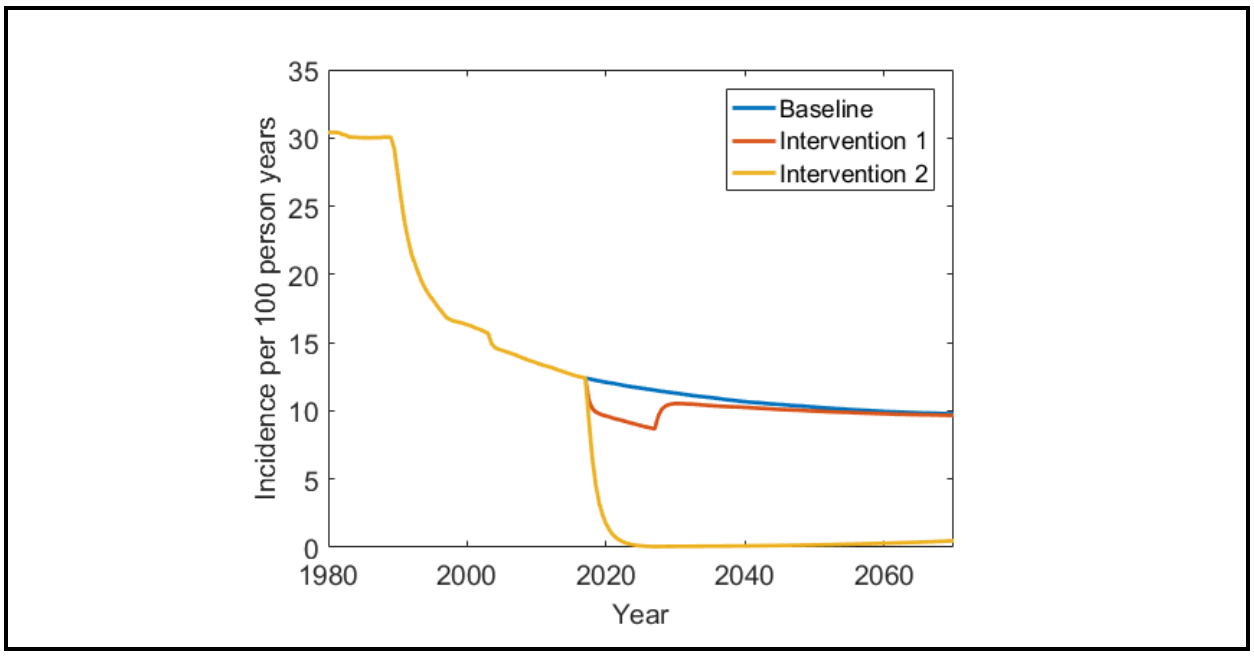


Table A3-2. Sensitivity Analysis for Baseline and MAT+SSP scale-up with HCV Screening and Treatment Scenarios

	Kentucky			San Francisco		
	Baseline (a)	**MAT+SSP with HCV Screen and Treatment (b)**	**Incremental (b vs. a)**	**Baseline (a)**	**MAT+SSP with HCV Screen and Treatment (b)**	**Incremental (b vs. a)**
Base-case						
Number of infections	4,158	2,306	-1,852	42,221	5,748	-36,473
Life-years	159,704	165,071	5,367	2,273,503	2,450,136	176,632
QALYs	46,779	49,874	3,095	706,637	785,576	78,939
Cost, $	42,870,668	64,456,601	21,585,932	1,610,582,798	2,482,369,200	871,786,402
ICER, $/ QALY	n/a	n/a	6,975	n/a	n/a	11,044
Reduce DAA costs by 25%						
Number of infections	4,158	2,306	-1,852	42,221	5,748	-36,473
Life-years	159,704	165,071	5,367	2,273,503	2,450,136	176,632
QALYs	46,779	49,874	3,095	706,637	785,576	78,939
Cost, $	39,575,973	56,050,953	16,474,980	1,566,710,810	2,192,029,431	625,318,621
ICER, $/ QALY	n/a	n/a	5,323	n/a	n/a	7,922

	Kentucky			San Francisco		
	Baseline (a)	**MAT+SSP with HCV Screen and Treatment (b)**	**Incremental (b vs. a)**	**Baseline (a)**	**MAT+SSP with HCV Screen and Treatment (b)**	**Incremental (b vs. a)**
Reduce DAA costs by 50%						
Number of infections	4,158	2,306	-1,852	42,221	5,748	-36,473
Life-years	159,704	165,071	5,367	2,273,503	2,450,136	176,632
QALYs	46,779	49,874	3,095	706,637	785,576	78,939
Cost, $	36,281,278	47,645,306	11,364,028	1,522,838,822	1,901,689,662	378,850,839
ICER, $/ QALY	n/a	n/a	3,672	n/a	n/a	4,799
Reduce DAA costs by 75%						
Number of infections	4,158	2,306	-1,852	42,221	5,748	-36,473
Life-years	159,704	165,071	5,367	2,273,503	2,450,136	176,632
QALYs	46,779	49,874	3,095	706,637	785,576	78,939
Cost, $	32,986,583	39,239,659	6,253,076	1,478,966,835	1,611,349,893	132,383,058
ICER, $/ QALY	n/a	n/a	2,020	n/a	n/a	1,677
SVR rate reduction						
Number of infections	4,158	2,640	-1,519	42,221	8,192	-34,029
Life-years	159,604	164,906	5,302	2,271,464	2,447,006	175,542

	Kentucky			San Francisco		
	Baseline (a)	**MAT+SSP with HCV Screen and Treatment (b)**	**Incremental (b vs. a)**	**Baseline (a)**	**MAT+SSP with HCV Screen and Treatment (b)**	**Incremental (b vs. a)**
QALYs	46,749	49,722	2,973	705,747	783,532	77,785
Cost, $	44,867,644	73,075,368	28,207,724	1,637,403,728	2,718,696,042	1,081,292,314
ICER, $/ QALY	n/a	n/a	9,489	n/a	n/a	13,901
Total 35 years						
Number of infections	2,424	668	-1,755	24,809	2,773	-22,035
Life-years	68,584	69,379	794	1,155,345	1,205,494	50,150
QALYs	29,438	31,170	1,732	499,607	545,239	45,632
Cost, $	21,525,634	59,195,897	37,670,264	1,184,766,020	2,329,418,562	1,144,652,542
ICER, $/ QALY	n/a	n/a	21,744	n/a	n/a	25,084
Total 110 years						
Number of infections	7,627	5,781	-1,846	76,916	25,819	-51,097
Life-years	414,734	445,411	30,677	5,030,247	5,662,504	632,257
QALYs	63,299	68,258	4,959	882,665	997,995	115,330
Cost, $	66,350,126	77,870,935	11,520,809	1,933,150,429	2,595,895,269	662,744,840
ICER, $/ QALY	n/a	n/a	2,323	n/a	n/a	5,746

	Kentucky			San Francisco		
	Baseline (a)	**MAT+SSP with HCV Screen and Treatment (b)**	**Incremental (b vs. a)**	**Baseline (a)**	**MAT+SSP with HCV Screen and Treatment (b)**	**Incremental (b vs. a)**
45% screen and 45% treat						
Number of infections	4,158	3,442	-716	42,221	27,660	-14,561
Life-years	159,704	163,954	4,261	2,273,503	2,411,675	138,172
QALYs	46,779	49,093	2,314	706,637	767,436	60,798
Cost, $	42,870,668	71,197,732	28,327,064	1,610,582,798	2,498,597,698	888,014,900
ICER, $/ QALY	n/a	n/a	12,240	n/a	n/a	14,606
Lower utility estimates (based on Wittenberg)						
Number of infections	4,158	2,306	-1,852	42,221	5,748	-36,473
Life-years	159,704	165,071	5,367	2,273,503	2,450,136	176,632
QALYs	42,009	45,050	3,041	597,387	671,510	74,123
Cost, $	42,870,668	64,456,601	21,585,932	1,610,582,798	2,482,369,200	871,786,402
ICER, $/ QALY	n/a	n/a	7,098	n/a	n/a	11,761
Minimum method for calculating QALYs						
Number of infections	4,158	2,306	-1,852	42,221	5,748	-36,473
Life-years	159,704	165,071	5,367	2,273,503	2,450,136	176,632

	Kentucky			San Francisco		
	Baseline (a)	**MAT+SSP with HCV Screen and Treatment (b)**	**Incremental (b vs. a)**	**Baseline (a)**	**MAT+SSP with HCV Screen and Treatment (b)**	**Incremental (b vs. a)**
QALYs	49,353	51,934	2,581	779,307	846,059	66,752
Cost, $	42,870,668	64,456,601	21,585,932	1,610,582,798	2,482,369,200	871,786,402
ICER, $/ QALY	n/a	n/a	8,363	n/a	n/a	13,060
Minimum method for calculating QALYs with lower utility estimates						
Number of infections	4,158	2,306	-1,852	42,221	5,748	-36,473
Life-years	159,704	165,071	5,367	2,273,503	2,450,136	176,632
QALYs	43,930	46,599	2,668	648,194	711,819	63,625
Cost, $	42,870,668	64,456,604	21,585,932	1,610,582,798	2,482,369,200	871,786,402
ICER, $/ QALY	n/a	n/a	8,089	n/a	n/a	13,702
No cost of pre-test counselling						
Number of infections	4,158	2,306	-1,852	42,221	5,748	-36,473
Life-years	159,704	165,071	5,367	2,273,503	2,450,136	176,632
QALYs	46,779	49,874	3,095	706,637	785,576	78,939
Cost, $	42,825,734	64,212,828	21,387,093	1,610,008,247	2,477,766,823	867,758,576
ICER, $/ QALY	n/a	n/a	6,910	n/a	n/a	10,993

	Kentucky			San Francisco		
	Baseline (a)	**MAT+SSP with HCV Screen and Treatment (b)**	**Incremental (b vs. a)**	**Baseline (a)**	**MAT+SSP with HCV Screen and Treatment (b)**	**Incremental (b vs. a)**
Increase in linkage to treatment after screening (53.8% treated, for diagnosed persons who formerly injected drugs)						
Number of infections	4,158	2,306	-1,852	42,221	5,748	-36,473
Life-years	161,496	165,308	3,812	2,306,149	2,455,032	148,883
QALYs	47,382	49,980	2,598	716,093	787,445	71,353
Cost, $	56,383,220	68,116,237	11,733,017	1,740,223,335	2,501,965,161	761,741,825
ICER, $/ QALY	n/a	n/a	4,516	n/a	n/a	10,676
Increased mortality in first four weeks after starting/cessating MAT						
Number of infections	4,154	2,294	-1,860	42,113	5,709	-36,404
Life-years	159,367	163,917	4,550	2,264,177	2,434,186	170,009
QALYs	46,684	49,484	2,800	704,024	780,556	76,532
Cost, $	42,700,265	63,923,500	21,223,235	1,602,064,903	2,469,822,936	867,758,033
ICER, $/ QALY	n/a	n/a	7,581	n/a	n/a	11,338
Decreased prevalence estimate among those aged over 50 (San Francisco only)						
Number of infections	n/a	n/a	n/a	21,009	1,319	-19,690
Life-years	n/a	n/a	n/a	1,778,346	1,920,192	141,846

	Kentucky			San Francisco		
	Baseline (a)	**MAT+SSP with HCV Screen and Treatment (b)**	**Incremental (b vs. a)**	**Baseline (a)**	**MAT+SSP with HCV Screen and Treatment (b)**	**Incremental (b vs. a)**
QALYs	n/a	n/a	n/a	573,519	634,406	60,886
Cost, $	n/a	n/a	n/a	1,317,141,430	2,141,333,899	824,192,469
ICER, $/ QALY	n/a	n/a	n/a	n/a	n/a	13,537

HCV = hepatitis C virus; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SSP = syringe-service program